J. Perinat. Med.
1 (1973) 114

The intensive care of perinatal risk in pregnant diabetics (136 cases): A new therapeutic scheme for the best control of maternal disease

Gian Domenico Roversi, Vittorio Canussio, Mario Gargiulo, Giovanni Battista Candiani

Institute of Obstetrics and Gynecology "L. Mangiagalli", University of Milan, 1st Department (Director: Prof. Dr. G. B. Candiani)

Received September 17, 1972. Accepted January 17, 1973.

Fifty years have elapsed since the discovery of insulin; however, pregnancy is still far from being sufficiently safe in diabetic women. The most convincing proof is given by the **high perinatal mortality ranging from 10 to 15% in specialized departments** [16], which would be even higher if therapeutic abortion was not performed in numerous cases of severe maternal disease [3, 11, 23]. On the other hand, as far as the mother is concerned, **insulin therapy has deeply changed the prognosis of pregnant diabetic patients** compared with the preinsulin era. However, severe complications such as toxemia, urinary tract infections, aggravation of vascular diseases and so forth contribute to maintain the death rate at about 1% [16, 23].

1. The problem of metabolic balance

In an extensive review of the problem it has already been emphasized, many years ago [10], that **unfavourable development of pregnancy and high perinatal mortality are associated specially with pregnant women lacking a good metabolic balance.** These findings were subsequently confirmed [16, 23] so that one may wonder whether in cases, considered to have been compensated for but still showing a high perinatal mortality rate, an actual optimal compensation had been obtained or whether its further improvement might have ameliorated fetal prognosis. As a matter of fact, the treatment of pregnant or non-pregnant diabetic patients is carried out everywhere by **regulating the insulin dosage on the basis of glycemia and glycosuria.** The difficulties found in establishing the degree of metabolic compensation by means of these indices caused a considerable discrepancy of opinion as to the optimal values for the **best therapeutical approach** [6, 16, 19, 23, 35, 37]. On the other hand, it may be debatable whether such a criterion represents an "optimum" for the feto-placental unit in considering that the features of newborns of **diabetic** mothers frequently appear even in newborns of **prediabetic** mothers, where blood sugar levels show little or no alteration; interesting results were obtained by insulin therapy in these cases [14, 22, 25, 41].

On the basis of the aforesaid considerations we began our investigations for a stricter control of diabetes mellitus in pregnancy in 1963. There-

Curriculum vitae

GIAN DOMENICO ROVERSI *was born in Milan in 1933, obtained his medical degree in 1958 and was lecturer in the First Clinic of Obstetrics and Gynecology, University of Milan, where he at first studied the steroid biosynthesis of various endocrine glands "in vitro". His investigations on diabetes mellitus in pregnancy were followed more recently by those on acid-base balance of the fetus during labor as well as by research on the use of ultrasounds in the study of fetal heart activity.*

fore, a new posologic criterion was adopted to control diabetes in pregnancy and, moreover, to avoid the possible over- and under-dosage of insulin [24, 25, 26, 27]. It will be illustrated below together with the obtained results.

2. Scheme of therapy

This scheme consists of progressively increasing amounts of insulin administered within 24 hours until the maximal tolerated dose is reached, the tolerance limit being indicated by **the appearance of the minor symptoms preceding the onset of hypoglycemia: perspiration** is the most evident and constant symptom among them*. The procedure for the administration of insulin is summarized in Tab. I; three black dots on the first line indicate the insulin dose taken by the patient before hospitalization (corresponding to 0 I.U., if the pregnant subject has not yet been given insulin).

Later on, each of the three daily amounts is **increased by 5 I.U. of fast-acting insulin** until the patients feels the first symptoms of hypoglycemia (perspiration). In the hypothetical case of the scheme, this occurs after having administered the morning insulin dose but it is quickly relieved by administering some lumps of sugar or, if necessary, intravenous glucose infusions. The insulin dosage is maintained unchanged on the following day in order to confirm the clinical symptom; thereafter, the morning dose of insulin is decreased by five units; in this way the **maximal tolerated dose of this administration is established.** The same procedure is applied in finding out the mid-day and evening dosages until the maximal tolerated dose is established.

Therefore, the **total amount of insulin varies from one pregnant patient to another;** however, it is regulated according to an identical clinical index, one which occurs also in healthy subjects after administration of a small dose of langerhansian hormone [27].

On admission to our department the patient choses her own diet without particular restrictions. This diet is then rigorously observed, care being taken as to caloric equivalence in the case of qualitative modifications.

Later on, **patients are discharged and checked weekly in the out-patient department;** during **periodical hospitalizations** in our department the insulin dose is adjusted to changes required during pregnancy according to our criterion [8, 16, 23].

3. Results

3.1 Diet

Our criterion made it possible to avoid numerous difficulties experienced in dietary prescriptions for diabetic patients as well as troubles occurring in pregnancy because of frequent food intolerance.

* This method of administering insulin can be defined also as pre-hypoglycemic insulin therapy, PHIT.

Tab. I. Scheme of followed insulin therapy; s. = sweating; m. t. d. = maximal tolerated dose.

Day	08.00 a. m.	12.00	07.00 p. m.
I	●	●	●
II	●+5 I. U.	●+5 I. U.	●+5 I. U.
III	●+5 I. U.	●+5 I. U.	●+5 I. U.
IV	●+10 I. U.	●+10 I. U.	●+10 I. U.
V	●+10 I. U.	●+10 I. U.	●+10 I. U.
VI	●+15 I. U. s.	●+15 I. U.	●+15 I. U.
VII	●+15 I. U. s.	●+15 I. U.	●+15 I. U.
VIII	●+10 I. U. m. t. d.	●+20 I. U.	●+20 I. U. s.
IX	●+10 I. U.	●+20 I. U.	●+20 I. U. s.
X	●+10 I. U.	●+25 I. U.	●+15 I. U. m. t. d.
XI	●+10 I. U.	●+25 I. U.	●+15 I. U.
XII	●+10 I. U.	●+30 I. U. s.	●+15 I. U.
XIII	●+10 I. U.	●+30 I. U. s.	●+15 I. U.
XIV	●+10 I. U.	●+25 I. U. m. t. d.	●+15 I. U.

After some days treatment it was necessary, in many cases, to reduce the amount of calories at the patient's request.

In addition, the influence of such a criterion concerning the **quantitative and qualitative composition of single diets was verified by means of further control examinations.** The average calorie amount administered in 24 hours was about **1,900 calories;** in most cases (Tab. II) the calories were kept within the limits of ±20% as compared with the individual requirement [34] corresponding to the needs of a resting and moderately working subject.

As for the calorie percentage on the average the diet was composed (Tab. III) of **15.5% of protides, 53.2% of glucides and 31.3 of lipids,** with oscillations of ± 10% in the majority of cases.

3.2 Insulin requirement

In the course of pregnancy a **progressive increase in insulin requirement** was always observed. At term of gestation this increase reached about 50 units of insulin daily over and above the maximal dose tolerated in the first trimester of pregnancy (Fig. 1).

Immediately after delivery it was always necessary to reduce the insulin dosage; in particular, insulin had to be discontinued in the majority of cases belonging to WHITE's class A [38] (Tab. IV). No pregnant patient was found to be insulin resistant according to WHO's definition [40].

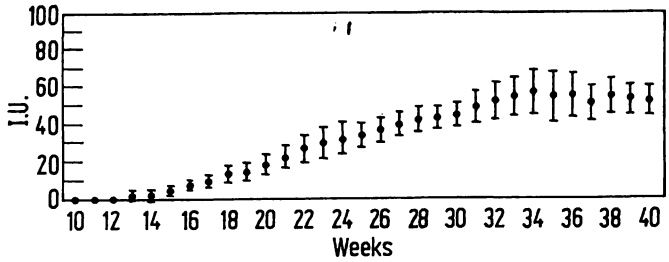


Fig. 1. Increase of insulin requirement during pregnancy.

Tab. IV. Distribution of case report according to WHITE's classification [38] and by trimester in which compensation was achieved.

Class	Trimester I	Trimester II	Trimester III	Total
A	4	13	31	48
B	12	20	16	48
C	4	8	7	19
D	4	3	3	10
F	4	1	6	11
	28	45	63	136

Tab. II. Distribution of cases reported according to the difference in percentage between calories supplied with diet and daily calorie requirement as calculated individually according to VANZETTI and GATTI's nomogram [34].

Difference between calories of diet and ideal requirement	±10%	±20%	±30%
Cases	64.5%	26.7%	8.8%

3.3 Case report

It includes 136 pregnant women treated according to the above-mentioned scheme. Tab. IV subdivides the patients according to the severity of diabetes [38] and the trimester of beginning treatment. WHITE's class A includes pregnant women with pregnancy diabetes and with latent diabetes, i. e. with reduced tolerance to glucose (capillar blood sugar level superior to 140% 120 min after an oral load of 50 g of glucose).

Tab. III Average composition of diet and percentage of cases with differences of ± 10%, ± 20%, ± 30% as compared with the mean values of each component.

	Average percentage composition of diet	Percentage of cases with differences of ±10%	Percentage of cases with differences of ±20%	Percentage of cases with differences of ±30%
Protides	15.53%	71.1%	24.4%	4.5%
Glucides	53.17%	71.1%	26.7%	2.2%
Lipids	31.30%	53.3%	37.8%	8.9%

3.4 Time of delivery

Pregnant women were controlled by determining **urinary estriol** [5] and in the last five years by **amnioscopy** [28]. Delivery was **never anticipated** by inducing labor or performing a Caesarean section; delivery occurred beyond the 37th week of pregnancy in 89% of the cases and beyond the 40th week in 13% (Tab. V).

3.5 Type of delivery

Vaginal delivery in 75% of the cases (Tab. VI) with application of **vacuum extractor in 8.8%.** In **25% of** the cases **Caesarean sections** were indicated, **when labor had started spontaneously;** 26.4% of those were multiparae already previously submitted to Caesarean section.

In the last three years fetal conditions during labor were controlled by **micro blood sampling** [29, 30] and by **continuous recording of fetal heart rate** [15]. Determinations of pH values in fetuses (Fig. 2) evidence only a **moderate degree of acidosis of maternal origin** [1] as shown by comparing the metabolic component of the acid-base balance of the mother with that of the fetus [29, 31]. Marked acidosis occurred during the second stage of labor only in two cases; these were complicated by a true knot and by premature separation of the placenta after hypertension of pregnancy due to adrenal adenoma respectively.

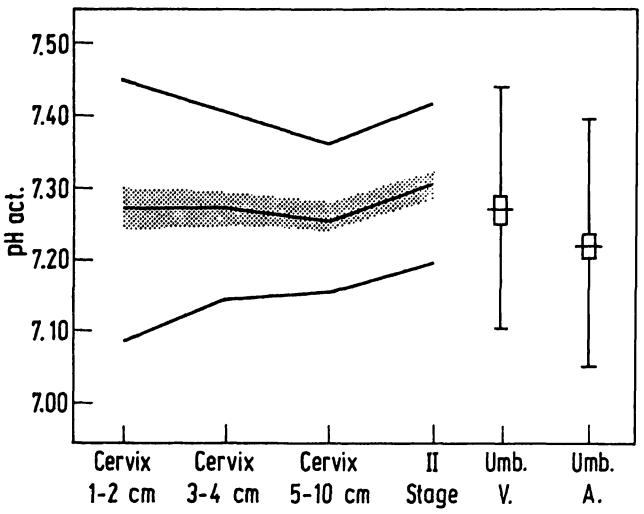


Fig. 2. Actual pH of fetus during labor (number of cases: 44; number of blood samples: 120). Mean values ± 2 sd (continuous lines) and 95% confidence limits of the mean (shaded area).

3.6 Weight of newborns

The curve of distribution of weight in newborns (Tab. VII) shows that in **81% of the cases the weight ranged from 2,500 to 4,000 g** and **exceeded 4,000 g only in 7.2% of the infants.** Babies weighing less than 2,500 g are those born within the 37th week of pregnancy.

3.7 Perinatal mortality and malformations in multiparae

Perinatal mortality among patients belonging to WHITE's class A and WHITE's classes B, C, D and F was in previous pregnancies 26.7% and 37.3% respectively, whereas **no case of fetal-neonatal death** was observed during these pregnancies (Tab. VIII).

Tab. V. Distribution of cases reported according to time of delivery.

Weeks of amenorrhea	No. of cases	%
34	1	0.7
35	2	1.5
36	4	2.9
37	8	5.9
38	27	19.9
39	26	19.1
40	50	36.8
41	7	5.1
42	11	8.1

Tab. VI. Classification of cases according to the mode of delivery.

Spontaneous	66.2%	
Vacuum extractor	8.8%	75.0%
Caesarean section		25.0%

Tab. VIII. Distribution weight at birth.

Weight (g)	No	%
1,500—2,000	4	2.9
2,001—2,500	12	8.7
2,501—3,000	32	23.2
3,001—3,500	55	39.9
3,501—4,000	25	18.1
4,001—4,500	7	5.1
4,501—5,000	1	0.7
5,001—5,500	2	1.4

Tab. VIII. Comparison of perinatal mortality and incidence of malformations between present and previous pregnancies in multiparae of our series distributed according to WHITE's classification [38].

Class		Number of newborns	
		Previous pregnancies	Present pregnancy
A	Sum:	45	24
	Alive not malf.	33 (73.3%)	24
	Alive malformed	0	0
	Dead not malf.	9 (20.0%)	0
	Dead malformed	3 (6.7%)	0
B+C+D+F	Sum:	118	59
	Alive not malf.	71 (60.2%)	57 (96.6%)
	Alive malformed	3 (2.5%)	2 (3.4%)
	Dead not malf.	37 (31.4%)	0
	Dead malformed	7 (5.9%)	0

Tab. IX. Total perinatal mortality and its distribution (in brackets the number of deaths) according to trimester of beginning of treatment and to WHITE's classification [38].

Class	Trimester			Total
	I	II	III	
A	4 (0)	13 (1)	32 (1)	49 (2)
B	12 (0)	20 (0)	17 (0)	49 (0)
C	4 (0)	8 (0)	7 (0)	19 (0)
D	4 (0)	3 (0)	3 (0)	10 (0)
F	4 (0)	1 (0)	6 (2)	11 (2)
	28 (0)	45 (1)	65 (3)	138 (4) = 2.9%

As regards the incidence of malformation a case of syndactylia with partial lack of both first phalanges in the right hand and a case of stenosis of the pulmonary artery occurred in multiparae while in previous pregnancies the total **incidence of malformations incompatible with life reached about 6%; the malformations compatible with life occurred in 2.5%** of newborns of mothers belonging to WHITE's classes B, C, D and F.

3.8 Perinatal mortality*

Only four cases of fetal and neonatal death occurred among our patients in this series, giving a perinatal **mortality of 2.9%**.

If the cases are classified according to the trimester in which pregnant patients were compensated following PHIT (Tab. IX) it can be seen, that no case of perinatal death occurred in patients treated from the first trimester; only one case was observed among patients treated from the second trimester and, perinatal mortality actually increased in the group of patients treated only since the third trimester.

The distribution of mortality was shown to be exclusively within in the classes A and F of WHITE's classification.

From the analysis of the four cases of fetal-neonatal death it should be noted that as regards the patient belonging to WHITE's class A and treated since the second trimester, the intrauterine death was due to prolapse of the cord after premature rupture of the membranes at the 35th week of pregnancy.

In two other cases, belonging to WHITE's class A and F, the cause of intrauterine fetal death could be attributed to toxemia, whereas in the last case the newborn died on the 8th day because of neonatal infection from herpes virus.

3.9 Therapeutic abortion

Therapeutic abortion was **never** performed even when patients were sent to our department with

* Perinatal mortality was calculated including the neonatal period until the time of discharge of infants from hospital.

the indication for this operation because of severe vascular complications.

3.10 Toxemia and fetal malformations

Toxemia was observed as a complication in eight cases **(5.8%),** four of which belonging to WHITE's class F and four subdivided among WHITE's remaining classes. Only in two cases belonging to WHITE's class A and F respectively, did toxemia set in with such serious symptoms as to be defined "severe" [23].

Malformations occurred in 2.9% of cases. None of them was incompatible with life and, to be precise, consisted of a supernumerary finger of the right hand and a partial defect of ossification of the frontal bone.

4. Discussion

The above-mentioned results show that the condition of pregnant diabetic patients — no matter how serious their metabolic disorder is — can be brought to a **normal state** as far as the development and result of pregnancy are concerned.

In this respect, two elements proved to be indispensable. The first one is the administration of insulin according to a criterion which assures a constant metabolic compensation during pregnancy; that means **not only a blood sugar balance but also an insulin balance,** where the further administration of insulin would have the same effect as on a non-diabetic subject. The second one is the **intensive care of patients frequently supervised by a specialist.** In fact, we never had to apply the measures generally used in the treatment of pregnancies of diabetics, namely therapeutic abortion in cases with severe vascular complications, hormonal prophylaxis and interruption of pregnancy at the 36—37th week by induction of labor or Caesarean section. Likewise no preventive care was taken in order to prevent conception, such as the use of contraceptives or surgical sterilization.

4.1 Results in terms of perinatal mortality

Perinatal mortality, which represents the index of pre-eminent interest in diabetic patients, is in the cases we reported **reduced to values which can also be accepted for pregnancies not at risk.** It should be noted that 30% of patients belong to WHITE's classes C, D and F, i. e. those offering minor probabilities of survial for fetuses. Moreover, pregnant diabetic patients treated within the 26th week of pregnancy show a perinatal mortality of 1.73% because of a case of prolapse of the cord in the 35th week of pregnancy.

4.2 Results in fetal weight

The considerable **decrease in perinatal mortality and in fetal macrosomia as evidenced by the cases we reported confirms their direct connection with the degree of maternal metabolic compensation** during the pregnancy as supported by various authors [7, 10, 16, 19, 23]. Moreover according to our data, the incidence of macrosomia seems to be further reduced whenever the mother's insulin deficiency is compensated for in early pregnancy. As a matter of fact, none of the 73 pregnant women treated since the first two trimesters gave birth to infants weighing more than 4,500 g and only two (2.7%) between 4,000 and 4,500 g; on the contrary, 65 patients treated only since the third trimester gave birth to 5 infants (7.7%) weighing 4,000—4,500 g and to 3 (4.6%) weighing more than 4,500 g.

4.3 Incidence of congenital malformations

The incidence of congenital malformations of fetuses is reduced in our case report and corresponds practically to that reported for normal pregnant women [16, 23]; this is undoubtedly an extremely interesting result because the high percentage of fetal malformations, especially in the case of vascular complications [20], is one of the major problems for pregnant diabetic patients. Moreover we have to bear in mind the **teratogenic effect of high doses of insulin in animals** [4, 33], the frequent findings of fetal malformations in pregnant women undergoing insulin shock therapy because of mental disorders at the beginning of pregnancy [17, 18] and the high incidence (34.2%) of hypoglycemia in the 1st trimester shown by pregnant women who gave birth to malformed fetuses [12]. It is therefore necessary to adopt a scheme for an insulin treatment assuring not only an excellent

metabolic compensation but also the **prevention of harmful hypoglycemic accidents in pregnant diabetic patients.**

4.4 Importance of severity of maternal disorder

The outstanding importance of mother's metabolic compensation as to the result of pregnancy is confirmed also by the lack of interrelation that we were able to observe between fetal risk and severity of maternal disorder; as a matter of fact, the incidence of perinatal mortality as well as of all manifestations indicated as diabetic fetopathy **do not increase** from WHITE's class A to F as reported in literature [16, 23].

On the contrary, the manifestation of late toxemia seems to bring a considerable increase in fetal risk as mentioned above [19, 23]; in point of fact, two of the four lethal cases occurred in pregnant women with severe signs of toxemia (1 case of WHITE's class A and another of WHITE's class F).

In pregnant women affected with extremely severe diabetes (WHITE's class D and above all WHITE's class F) the problem of clinical approach which proves difficult because of the high perinatal mortality is furthermore complicated by a progressive worsening of vascular disease as frequently observed in the course of pregnancy [13, 21, 23, 39] so that therapeutic abortion may be often considered necessary. In our experience we never found a tendency to such a worsening of retinopathy of patients belonging to WHITE's class D and F [36]; thereafter, there is evidence of a favourable development of pregnancy for both mother and fetus, and the practice of therapeutic abortion in these cases has to be accepted with greater reservations [16, 23].

4.5 Treatment of latent diabetes

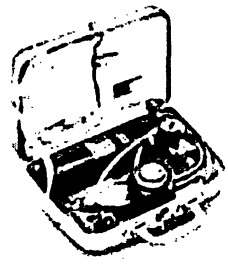
The group of pregnant women belonging to WHITE's class A commands particular attention. There is in the literature a **divergence of opinion about the treatment of latent diabetes in pregnancy** [16, 23]. As previously observed by some authors [14, 22, 41], and according also to our results, **the insulin treatment can decrease the neonatal weight and the perinatal mortality in pregnant women affected with this type of diabetes.** In fact, the perinatal mortality of 24 multiparae belonging to WHITE's class A reached 25% in former pregnancies whereas no case of death occurred in these pregnancies and the weight of newborns never exceeded 4,000 g. Authors carrying out insulin therapy in pregnant women with latent diabetes [14, 22, 41] cannot use blood and urinary sugar levels as referrant parameters. Therefore, they rely upon their own precautionary criteria and establish a priori in all these cases the same insulin dosage, which obviously proves unable to achieve uniform and excellent metabolic balance in all instances. These inconveniences and troubles can be overcome by applying our scheme which is suitable also for pregnant women with latent diabetes where it proves to be of great value in setting up a clinical index for blood and urinary sugar levels in monitoring insulin therapy.

Sweating appears to be the earliest and most steady symptom when in non-diabetic subjects the normal balance is modified by fasting or by administering small doses of insulin. Severe hypoglycemic crises can be avoided with certainty by applying such a scheme causing sweating because the amount of insulin is increased by only 5 I.U. in each of three injections.

Likewise, after discharge from our department **no cases of hypoglycemic coma** — usually not rare in diabetic pregnancy — were observed, because the final dose (maximal tolerated dose) is established by reducing the dose causing sweating by 15 I. U. of insulin (5 for each series). Also the prevention of acidosis or diabetic precoma seems in our cases an important result if one considers their well-known influence in worsening the prognosis of the fetus [23]. The 24-hour blood sugar levels (at 4.00, 8.00, 12.00, 16.00, 20.00, 24.00 hours) after having reached the balance showed values within normal limits.

4.5 Antenatal care

Therefore, a **program of intensive care with weekly follow-ups in the out-patient department** and, if necessary, **short periods of hospitalization** proved to be indispensable for adjusting the maximal tolerated dose to the well-



Alternating Pressure Respirator for New-Born Babies (according to Saling)

THE AUER WB66 BRINGS YOU UP TO DATE WITH PERINATAL MEDICINE

When reanimating asphyxia newborns a rapid insufflation of oxygen is indicated. This can be done with our alternating pressure respirator, which helps you in treating hypoxia and acidosis of newborns.

The respirator is called WB 66 and is built according to Prof. Saling. It is easy and safe in its application - much more so than the WB 58 from which we developed it. The WB 66 ensures a full-fledged endotracheal respiration with oxygen or air under alternating pressure. The unit is so handy that you may take it along. This is only one of its advantages. What else is new with the AUER WB 66 our technical leaflet will tell you. Just mail us the coupon.

Please send me your technical leaflet for the AUER WB 66

Name_____

Company_____

Street_____

City_____ Zip code_____

Auergesellschaft GmbH, Medizintechnik
D1 Berlin 65, Friedrich-Krause-Ufer 24-34

We protect people and their work.

AUER

2372004E

H. Rainer Maurer

Disc Electrophoresis

and Related Techniques of Polyacrylamide Gel Electrophoresis

Second revised and expanded edition. 1971. XVI, 222 pages. With 88 figures, 16 tables and 948 literature references
Bound DM 68,—; $ 25.25
ISBN 3 11 003495 6
(Working Methods in Modern Science. Edited by Prof. Dr. K. Fischbeck)

This updated and revised monograph in Englich language brings together — as far as possible — the body of widely dispersed knowledge and experience obtained from methods in disc electrophoresis and related techniques of polyacrylamide gel electrophoresis. The book is intended as a laboratory manual which, in addition, will spare the user time-consuming literature study and technical errors as much as possible.
Included are exact procedures for the most varied separation problems, a survey of types of apparatus, descriptions of methods for detection and quantitation of proteins, nucleic acids, enzymes, antigens and radioactivities, a detailed treatment of micro disc electrophoresis, preparative polyacrylamide gel electrophoresis and many other techniques for special problems. In addition, this monograph also cites examples of results from research in biochemistry, clinical chemistry and food technology with the intention of offering suggestions and showing the versatility of the method. From the information in this book, the user should be able, without any previous experience, to solve his separation problems to his (her) satisfaction.

known increase in insulin requirement during pregnancy. At any rate, we were able to observe cases requiring a frequent increase in maximal tolerated dose up to delivery as contrasted to other ones in which the dose has to be kept unchanged over much longer periods of time.

As for the diet, the idea of choosing the diet herself had a **positive psychological effect** on the patient, but in most cases the free diet corresponded in the quantitative and qualitative composition to the theoretical requirements (Tabs. II to III).

4.7 Delivery time of diabetics

At the present, the opinions reported in the literature as to the most convenient time of delivery for diabetic pregnant patients are not standardized. The induction of delivery at the 36—37th week of gestation, as recommended by most authors [10, 11, 16, 23, 38] because of the high perinatal mortality in the last month, is in the opinion of others [2, 19, 32] not necessary for pregnant patients at term who have been well regulated and have had no complications of pregnancy.

In our series delivery was never induced but **started spontaneously and in some cases beyond the presumed term.** In the course of labor only slight diminution of pH values due to the passage of fixed acids from mother to fetus has to be pointed out [29]; this acidosis, however, never caused severe problems at birth.

Although not forming part of the purpose of this work, we cannot ignore in our conclusions the problems of the **pediatrician** attending the newborn of diabetic mother: the results of a previous series of own cases [9] did not substantially change, i. e. the particular clinical and humoral phenomenology of the newborn of diabetic women occurred in a very small percentage of cases and, moreover, in such a way as to be easy to control.

4.8 Conclusion

Our results obtained since 1963 in the treatment of pregnant diabetic patients have been repeatedly reported [25, 26, 27]. In consideration of the paramount importance of results as to the appraisal of therapy, their constant positive outcome strongly suggest that the **theoretical premises of PHIT have been confirmed,** i. e. the necessity of achieving in pregnant diabetic patients a metabolic compensation so that both administered and endogenous insulin may correspond to the requirements of the organism. The **easy handling** together with the **ease of avoiding accidents** due to under- or overdosage of insulin makes it possible to carry out intensive care of pregnant diabetic women even where **no specialized centres** are available.

Summary

According to the literature, at an appraisal "a posteriori" **fetal risk in pregnant diabetic patients appears to be always reduced by a good control of maternal disorder.** However, the various authors are of quite different opinions as to the value to be attributed to the indices of carbohydrate metabolism in insulin-compensated pregnant diabetic patients so that it seems difficult "a priori", i. e. during pregnancy, to guarantee a successful treatment for the fetus. On the other hand, the problem becomes complicated if one also considers the high risk for fetuses of pregnant women affected with latent diabetes.

Therefore, since 1963 a particular therapeutical criterion has been adopted: fast-acting insulin was administered in three daily injections at continuously increasing doses. When early hypoglycemic troubles (sweating, feeling of hunger and so forth) set in, the excess dose was reduced **(Tab. I).**

At the admission to our department the diet was chosen by the patient without particular restrictions and then rigorously observed with regard to caloric equivalence in the case of qualitative modifications. In most cases that diet corresponded quantitatively and qualitatively to the theoretical requirements of the pregnant patients **(Tabs. II to III).**

Weekly control examinations and eventual short periods of hospitalization proved to be necessary in order to maintain a balance between the maximal tolerated dose, established during the first hospitalization, and the continuous increase **in insulin requirement during pregnancy (Fig. 1); the spontaneous onset of labor was always awaited (Tab. V)** and the **estriol in urine** was systematically determined; **amnioscopy** has been performed since 1967. **Vaginal delivery was observed in 75%** out of 136 cases **(Tab. VI),** 88 belonging to WHITE's classes B, C, D, F **(Tab. IV).** Determinations of pH values in fetuses **(Fig. 2)** evidenced only **a moderate degree of acidosis of maternal origin. Perinatal mortality amounted to 2.9% (Tab. IX),** the incidence of **macrosomia** (> 4,000 g) **was 7.2%**

(Tab. VII), toxemia occurred in 5.8% of the cases, and **malformations,** always compatible with life, in 2.9%.
The results show that the **fetal risk in pregnant diabetic patient can be deeply reduced maintaining a constant insulin balance.** The adopted scheme seems to fulfil these requirements and it can be realized without specialized centers. Moreover, it can also be applied to pregnant women with latent diabetes where, according to the experience of various authors, insulin therapy can reduce fetal risk **(Tabs. VIII to IX).**

Keywords: Diabetes, prediabetes, pregnancy, perinatal mortality, Insulin, pH, prehypoglycemia, toxemia, malformations.

Zusammenfassung

Die Intensiv-Überwachung der schwangeren Diabetikerin (136 Fälle): Ein neues therapeutisches Schema für die beste Kontrolle der mütterlichen Krankheit.
Nach Literaturangaben **nimmt das fetale Risiko bei der diabetischen Schwangeren mit der Güte der Kontrolle der mütterlichen Krankheit ab.** Allerdings gibt es Meinungsunterschiede unter den Autoren über die Einstellung der Parameter des Kohlenhydrat-Stoffwechsels bei der diabetischen Schwangeren, die zur optimalen Kompensation erreicht werden müssen. Es ist also schwierig während der Schwangerschaft, eine erfolgreiche Behandlung des Feten zu garantieren. Außerdem wird das Problem komplizierter, wenn man bedenkt, daß auch für Feten von Schwangeren mit einem latentem Diabetes ein hohes Risiko besteht.
1963 haben wir eine neue Behandlungsmethode vorgeschlagen. Alt-Insulin wird mit drei täglichen Spritzen in um 5 E. steigenden Dosen gegeben; wenn die ersten Zeichen der Hypoglykämie auftreten (leichtes Schwitzen, Hunger usw.) wird die Insulingabe um 5 Einheiten verkleinert, so wird die **tolerierte Maximaldosis** festgestellt **(Tab. I).**
Die Diät, die die Schwangeren in der Klinik erhalten haben, ist ohne besondere Einschränkungen. Die Kalorien bleiben bei qualitativen Änderungen gleich. In den meisten Fällen entspricht diese Diät sowohl quantitativ als auch qualitativ dem theoretischen Bedarf der Schwangeren **(Tab. II, III).**
Bei wöchentlichen Kontrollen und wiederholten Aufnahmen in die Klinik wurde die **Insulindosis an die Änderungen des Insulinbedarfs angepaßt (Abb. 1); nie haben wir die Schwangerschaft vorzeitig beendet (Tab. V),** und die Patientinnen wurden durch systematische Messungen der **Östriolausscheidung** und seit 1967 auch **amnioskopisch** überwacht.
Von 136 Fällen gehörten 88 zu den Klassen B, C, D und F nach White **(Tab. IV),** bei ungefähr **75% der Schwangeren wurde eine vaginale Entbindung** durchgeführt **(Tab. VI).** Die Bestimmung der fetalen Blut-pH-Werte **(Abb. 2)** zeigte nur eine begrenzte **Aziditätssteigerung mütterlichen Ursprungs.** Die **perinatale Mortalität betrug 2.9% (Tab. IX), Makrosomie** (> 4000 g) **7.2% (Tab. VII), Gestose 5.8%** der Fälle und die **Mißbildungen** (die nicht lebensgefährlich waren) **2.9%.**
Diese Resultate zeigen, daß das **Risiko der diabetischen Schwangeren und das Risiko des Feten einer diabetischen Schwangeren durch ein konstantes Insulin-Gleichgewicht beträchtlich gesenkt** werden kann. Dieses Problem wird durch die prähypoglykämische Insulin-Therapie gelöst, auch in nicht spezialisierten Zentren. Außerdem kann diese Methode bei Schwangeren mit latentem Diabetes angewandt werden, bei denen, wie verschiedene Autoren meinen, die Insulin-Therapie das fetale Risiko senkt **(Tab. VIII, IX).**

Schlüsselwörter: Diabetes, Prädiabetes, Schwangerschaft, perinatale Mortalität, Insulin, pH, Prähypoglykämie, Gestose, Mißbildungen.

Résumé

Soins intensifs et risque périnatal chez les femmes enceintes diabétiques (136 cas): un nouveau schéma thérapeutique pour le meilleur contrôle de la maladie maternelle.
Selon la littérature, **le risque foetal apprécié «a posteriori» chez les diabétiques enceintes semble être toujours réduit par un bon contrôle du désordre maternel.** Cependant, les différents auteurs ont des opinions tout-à-fait différentes sur la valeur à attribuer aux index du métabolisme des hydrates de carbone chez une diabétique enceinte équilibrée, de telle sorte qu'il semble difficile «à priori», par exemple pendant la grossesse, d'être assuré du succès du traitement pour le foetus. Par ailleurs, le problème se complique si l'on considère aussi le haut risque pour les foetus chez les patientes atteintes de diabète latent.
Ainsi, depuis 1963 un critère thérapeutique spécial a été adopté: de l'insuline ordinaire était administrée à raison de trois injections par jour à des doses constamment croissantes. Lorsque les premiers troubles hypoglycémiques (sueur, sensation de faim ou autres) apparaissaient, la dose était réduite **(Tab. I).**
A l'admission dans notre service, le régime était choisi par la patiente sans restrictions particulières et rigoureusement observé en tenant compte de l'équivalent calorique

dans le cas de modifications qualitatives. Dans la plupart des cas le régime correspondait à la composition quantitative et qualitative des besoins théoriques chez la femme enceinte **(Tab. II, III).**

Des contrôles hebdomadaires et éventuellement de courtes périodes d'hospitalisation se sont avérés nécessaires pour maintenir l'équilibre entre la dose maximale tolérée, établie au cours de la première hospitalisation, et l'augmentation continue du **besoin en insuline au cours de la grossesse (Fig. 1); on a toujours attendu le début spontané du travail (Tab. V) et les oestriols urinaires** étaient mesurés systématiquement; on a fait des **amnioscopies** depuis 1967.

On a observé 75% d'accouchements par voie basse sur 136 cas **(Tab. VI),** 88 appartenaient aux classes B, C, D, F **(Tab. IV).** La détermination des valeurs du pH chez le foetus **(Fig. 2)** a mis seulement en évidence une **acidose modérée d'origine maternelle. La mortalité périnatale a été de 2,9% (Tab. IX);** l'incidence de la **macrosomie** (> 4000 g) était de **7,2% (Tab. VII);** une **toxémie** est apparue dans **5,8%** des cas et des **malformations,** toujours compatibles avec la vie, dans **2,9%** des cas.

Les résultats montrent que **le risque périnatal chez les femmes enceintes diabétiques peut être fort reduit en maintenant un bon équilibre insulinique.** Le schéma adopté semble répondre à ces besoins et il peut être employé dans des centres pas spécialisés. D'ailleurs il peut aussi être appliqué aux femmes enceintes avec diabète latent chez lesquelles, selon l'expérience de différents auteurs, le traitement par l'insuline pourrait réduire le risque foetal **(Tab. VIII et IX).**

Mots-clés: Diabète, prédiabète, grossesse, mortalité périnatale, insulinothérapie, pH, préhypoglycémie, toxémie, malformations.

Acknowledgement

The authors are grateful to Miss Nella Castiglioni for her valuable collaboration in the care of diabetic mothers.

Bibliography

[1] Beard, R. W.: Maternal fetal acid-base relationship. In: Adamsons, K.: Diagnosis and treatment of fetal disorders. Springer, Berlin-Heidelberg-New York 1968

[2] Berger, M., U. Lewinski: Über 100 Fälle von Diabetes und Schwangerschaft. Gynaecologia 161 (1966) 105

[3] Brandstrup, E., M. Osler, J. Pedersen: Perinatal mortality in diabetic pregnancy. Acta endocr. (Kbh.) 13 (1961) 434

[4] Brinsmade, A., F. Büchner, H. Rübsamen: Mißbildungen am Kaninchenembryo durch Insulininjektion beim Muttertier. Naturwissenschaften 43 (1956) 259

[5] Bompiani, A., G. D. Roversi, M. Finelli, C. Aicardi: Valutazione della funzione feto-placentare nelle gravide diabetiche mediante correlazione della estrioluria e dell'istoplanimetria placentare. In: Atti del 1° Congresso Nazionale della Società Italiana di Diabetologia e del III° Simposio Nazionale sul Diabete, Catania 1968, Casa Ed. Il Ponte, Milano 1967

[6] Constam, G. R.: Der Diabetes während der Schwangerschaft. Praxis 55 (1966) 1356

[7] Daweke, H., K. A. Hüter, B. Sachsse, J. Gleiss, K. Jahnke, F. A. Gries, P. H. Werness, A. Irtel, V. Brenndorff, H. Idel, K. Becker: Diabetes und Schwangerschaft, Ursachen und therapeutische Beeinflußbarkeit der kindlichen Sterblichkeit. Dtsch. med. Wschr. 95 (1970) 1747

[8] Drury, M. I.: Pregnancy in the diabetic. Diabetes 15 (1966) 830

[9] Flauto, U., G. D. Roversi, C. Aicardi: Rilievi clinico-statistici a proposito di 39 nati da madri diabetische. Atti del 1° Congresso Nazionale della Società Italiana di Diabetologia e del III° Simposio Nazionale sul Diabete, Catania 1966, Casa Ed. Il Ponte, Milano 1967

[10] Gellis, S. A., D. Y.-Y. Hsia: The infant of the diabetic mother. Amer. J. Dis. Child. 97 (1959) 1

[11] Hagbard, L.: Pregnancy and Diabetes mellitus. Thomas, Springfield 1961

[12] Herre, H.-D., Z. Horky, U. Fischer: Kritische Bewertung der Geburtsleitung bei 160 diabetischen Schwangeren. Zbl. Gynäk. 87 (1965) 244

[13] Herre, H.-D.: Die diabetischen Mikroangiopathien in der Schwangerschaft. Zbl. Gynäk. 87 (1965) 1418

[14] Hoet, J. J.: Nouvelles recherches sur le diabète de la gestation. Memoires de L'Academie Royale de Medicine de Belgique 7 (1969) 116

[15] Hon, E. H.: Biophysical studies of the human fetus. In: Adamsons, K.: Diagnosis and treatment of fetal disorders. Springer, Berlin-Heidelberg-New York 1968

[16] Horký, Z., U. Fischer, E. Wappler: Schwangerschaft bei Diabetes mellitus. Fischer, Stuttgart 1969

[17] Impastato, D. J., A. R. Gabriel, H. H. Lardaro: Electric and insulin shock therapy during pregnancy. Dis. Nerv. Syst. 25 (1964) 542

[18] Mac Connell, J.: Two years experience of female schizophrenics treated by insulin coma therapy. J. Ment. Sci. 91 (1945) 506

[19] Möller, E.-B.: Studies in diabetic pregnancy. Studentenlitteratur, Lund 1970

[20] Mølsted-Pedersen, L., I. Tygtrup, J. Pedersen: Congenital malformations in newborn infants of diabetic women. Lancet 1 (1964) 1124

[21] Oakley, W. G.: The effect of Pregnancy on Diabetic Angiopathy. In: Oberdisse, K., K. Jahnke: Diabetes mellitus. III. Kongreß der International Diabetes Federation, Düsseldorf 1958. Thieme, Stuttgart 1959
[22] O'Sullivan, J. B., S. S. Gellis, R. V. Dandron, B. O. Tenney: The potential diabetic and her treatment in pregnancy. Obstet. Gynec. 27 (1963) 683
[23] Pedersen, J.: The pregnant diabetic and her newborn. Munksgaard, Copenhagen 1967
[24] Roversi, A. S.: Du traitment insulinique du diabète et de ses complications. La thérapie insulinique préhypoglycémisante (T. I. P. I). Press Méd. 12 (1957) 243
[25] Roversi, G. D., V. Canussio: Neue Aspekte der Diabetes Therapie in der Gravidität. In: Saling, E., F. J. Schulte: Perinatale Medizin. Band II. 3. Deutsche Kongreß für Perinatale Medizin, Berlin 1970. Thieme, Stuttgart 1972
[26] Roversi, G. D., C. Aicardi: La T. I. P. I. (Terapia insulinica pre-ipoglicemica) in ostetricia. Nuove prospettive terapeutiche della gravida diabetica. Ann. Ostet. Ginec. 87 (1965) 239
[27] Roversi, G. D., C. Aicardi: Nuove prospettive terapeutiche del diabete mellito in gravidanza (T. I. P. I). In: Atti del 1° Congresso Nazionale della Società Italiana di Diabetologia e del III° Simposio Nazionale sul Diabete, Catania 1966, Casa Ed. Il Ponte, Milano, 1967
[28] Roversi, G. D., V. Canussio: Die Amnioskopie in der Frühdiagnose der fetalen Hypoxie: Anwendung und Auswertung der Methode (1000 Fälle) Geburtsh. u. Frauenheilk. 29 (1969) 1005
[29] Roversi, G. D., V. Canussio: Relationship between fetal heart rate and acid-base balance during labor. In: Crosignani, P. G., G. Pardi: Fetal evaluation during pregnancy and labor. Academic Press, New York — London 1971
[30] Saling, E.: Das Kind in Bereich der Geburtshilfe, Thieme, Stuttgart 1966
[31] Saling, E.: Fetal blood studies. In: Huntingford, P. J., K. A. Hüter, E. Saling: Perinatal Medicine. 1st European Congress of Perinatal Medicine, Berlin 1968. Thieme, Stuttgart 1969
[32] Schwarz, R. H., G. A. Fields, G. C. Kyle: Timing of delivery in the pregnant diabetic patient. Obstet. Gynec. 34 (1969) 787
[33] Smithberg, M.: Teratogenic effects of some hypoglycemic agents in mice. Univ. Mich. Med. Bull. 33 (1961) 67
[34] Vanzetti, G., E. Gatti: Un nomogramma per il calcolo del fabbisogno calorico individuale. Dietol. e Dietoter. 2 (1958) 1
[35] Vedra, B., H. Pribylová, K. Zuamenácek: Die Prognose lebend geborener Kinder von Diabetikerinnen. Z. Geburtsh. Gynäk. 170 (1969) 83
[36] Vigorelli, E., G. D. Roversi, C. Aicardi: Evoluzione di complicanze vascolari retiniche di gravide diabetiche. In: Atti del 1° Congresso Nazionale della Società Italiana di Diabetologia e del III° Simposio Nazionale sul Diabete, Catania 1966, Casa Ed. Il Ponte, Milano 1967
[37] White, P.: Pregnancy and diabetes, medical aspects. Med. Clin. N. Amer. 49 (1965) 1015
[38] White, P.: Pregnancy complicating diabetes. Amer. J. Med. 7 (1949) 609
[39] White, P., L. Gillespie, L. Sexton: Use of female sex hormone therapy in pregnant diabetic patients. Amer. J. Obstet. Gynec. 71 (1956) 57
[40] W. H. O. Diabetes mellitus. Report of WHO expert committee, World Health Organization. Technical Series 310, 1965
[41] Wilkerson, H. L. C., Q. R. Remein: Studies of abnormal carbohydrate metabolism in pregnancy. Diabetes 6 (1957) 324

Prof. Dr. G. D. Roversi
Clinica Ostetrica e Ginecologica
"L. Mangiagalli"
Via della Commenda, 12
20122 Milano/Italia